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제어 방출형 매트릭스로서 키토산과 카보폴 복합체의 제조

朝鮮大學校 大學院

藥 學 科

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Preparation of chitosan/Carbopol complex as a controlled release matrix

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박 성 현

지도 교수 : 최 후 균

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최근들어 약물의 복용 횟수를 줄여주어 환자의 복약 순응도를 높여주고 혈중 농도의 변동을 줄여 부작용을 낮춰주는 장점을 갖는 제어 방출형 제형의 개발에 많은 관심이 집중되고 있다. 제어 방출형 제형을 개발하는데 있어서 구성 polymer의 특이적인 상호작용으로 인해 생성되는 interpolymer complex는 기존의 polymer와는 또 다른 특성을 지니기 때문에 연구원들의 많은 관심을 끌고 있다. 본 실험에서는 chitosan과 Carbopol interpolymer complex를 제어 방출형 제형의 기제로 사용하여 서방출형 matrix system을 개발하였다. Chitosan과 Carbopol의 interpolymer complex는 점막점착성, 팽윤성 및 산성 조건에서 녹는 성질을 갖고 있어서 기존에 점막점착성 필름, 점막점착성 미립구, 나노 입자제조와 위에서 제어 방출하는 matrix 등에 응용되어 왔다. 이 실험에서는 이런 특유의 특성을 가진 chitosan과 Carbopol interpolymer complex를 분말 상태로 제조하여 제어 방출형 정제를 제조하는데 사용될 직타용 부형제를 제조하고 theophylline과 정제를 타정하여 제어방출형 제형 제조의 가능성을 알아보는 실험을 하였다. Theophylline은 물에 8.3mg/ml의 용해도를 갖고 있으며 pH의 변화에 따라서 용해도 변화를 크게 받지 않는 약물로 알려져 있어서 모델 약물로 선정하였다.

Interpolymer complex를 제조하기 위해 Chitosan과 Carbopol 용액을 제조한 후 혼합

하여 생성된 흰색의 침전물을 건조하고 분쇄한다. 그리고 얻어진 분말의 성상을 FT-IR과 DSC을 이용하여 알아보았다. FT-IR을 통해서 interpolymer complex가 chitosan의 NH_3^+와 Carbopol의 COO^-의 정전기적 결합에 의해서 생성됨을 확인하였고 이렇게 생성된 interpolymer complex는 초기 물질과는 다른 열역학적 성질을 나타내었다. 그리고 탁도 측정을 통해서 interpolymer complex의 조성비를 조사한 결과 chitosan과 Carbopol이 1:4의 몰비로 결합되어 있음을 확인할 수 있었다.

이 complex로 제조된 정제의 제어방출 제형으로서의 특성과 약물의 방출 기전을 확인하기 위해서 pH 1.2와 6.8에서의 용출시험과 swelling과 erosion 시험을 진행하였다. 두 가지 용출액에서 interpolymer complex를 사용하였을때 Carbopol, chitosan, HPMC 2910을 사용하여 타정하였을 때보다 약물의 방출속도가 지연되는 것을 확인할 수 있었다. 용출실험 중인 정제의 사진을 확인한 결과 팽윤된 complex matrix 내부에 약물이 오래 보존됨으로 인해 약물이 제어 방출되었다. 용출 결과를 Kosmeyer식과 Peppas and Sahlin식에 적용 시켜본 결과 pH 1.2에서는 polymer relaxation에 의해서, pH6.8에서는 diffusion에 의해서 각각 약물이 방출됨을 확인하였다. 그리고 swelling과 erosion 시험을 통해서 이런 계산된 약물의 방출 기전을 다시 확인하였다.

이 결과 chitosan과 Carbopol로 제조된 interpolymer complex로 제조된 matrix는 complex가 swelling 되면서 약물이 빠져나가고 swelling된 gel 안에 약물이 오랜 시간 머물러 있음으로해서 장시간 약물을 제어 방출 하는 것을 확인하였다. 그리고 pH에 따라서 한 가지의 약물방출 기전이 적용되기 때문에 이를 조절하는데 다른 복합적인 기전을 갖는 제형보다는 장점을 갖을 것으로 판단된다.

Prepation of chitosan/Carbopol complex as a controlled release matrix

Abstract

The swellable matrix tablet using chitosan/Carbopol interpolymer complex (IPC) was prepared for controlling the release of a drug. Carbopol 971 was dissolved in distilled water and chitosan was dissolved in acetic acid, and then Carbopol solution and chitosan solution were mixed together. The resulting precipitate (chitosan/Carbopol IPC) was obtained. Various molecular weights of chitosan were used to prepare the complex. The formation of the complex through ionic interaction between Carbopol 971 and chitosan was investigated by monitoring the transmittance of the solution at a wavelength of 600 nm. Carbopol and chitosan solutions were mixed as a function of various repeating unit ratios (chitosan/Carbopol). To prepare swellable matrix tablet, the complex was ground using a ball mill and sieved through the pore size of 200 μm. The complex powders were compressed by a hydraulic press with a 13-mm die and flat-faced punches at a compression pressure of 10 kN/cm^2 with a dwell time of 1 s. Water uptake ratio of the complex tablets was measured using USP dissolution apparatus II (paddle method) with a rotating speed of 50 rpm at 37^oC. Complex formation was confirmed by FT-IR and turbidity. The turbidity measurement indicated that the ratio of chitosan/Carbopol to form the complex was 1/4. The extent of swelling was pH dependent and was greater than

1300% and 2000% at pH 6.8 and 1.2 medium, respectively. The release profile of theophylline as a model drug from the tablet was extended to 20 h. The release rate could not be controlled according to the molecular weight of chitosan. The main release mechanisms of complex tablet were diffusional release in pH 6.8 medium and relaxation of polymer in pH 1.2.

Key words

Chitosan; Carbopol; interpolymer complex; extended release

1. Introduction

Recently, interpolymer complex (IPC) attracts the attentions of pharmaceutical researchers [1], because it has unique characteristics due to the specific interaction between the constituent polymers such as hydrogen bond, electrostatic interaction, van der Waals force and hydrophobic interaction [2]. The approaches usually used in the preparing the IPC includes: (a) acidic polymer such as poly(acrylic acid), acting as proton-donating polymer, was applied to form IPC with nonionic proton-accepting polymers such as poloxamer and polysaccharides [3, 4]; (b) polycationic polymer such as chitosan was used for preparation of polyelectrolyte complex with polyanions as carboxymethylcellulose, alginic acid, pectin, xanthan and poly(acrylic acid) [5]. In this study, the latter approach was applied to prepare the IPC.

Chitosan [poly(1,4-β-D-glucopyranosamine)] is an amino polysaccharide polymer. It is obtained by the extensive deacetylation of chitin. This natural polysaccharide possesses some favorable properties, such as non-toxicity, high biodegradability and biocompatibility [6]. Chitosan has been investigated in oral drug delivery system like tablet, capsule, buccal disk, beads and film coating [7, 8]. Especially, it acts as disintegration agent [8], tablet binder [9] in tablet. Despite of these favorable properties and variable usages, chitosan was rarely used to prepare sustained release oral dosage form when separately used, due to its characteristics like water sorption, capillary action [8] and dissolving in gastric environment.

Carbopol is a polymer of acrylic acid and slightly crosslinked with allyl sucrose or allylpentaerythritol. In field of oral dosage form, Carbopol is among the most used excipients for preparing sustained release tablet [10]. Because the characteristics of Carbopol such as readily hydration, absorption of water and swelling to form a gelatinous network or barrier layer in aqueous solution made the tablet containing Carbopol release a drug in zero or near zero order profiles. [11, 12]

The IPC formation between chitosan and poly(acrylic acid) has been previously reported [13]. This IPC had characteristics like mucoadhesive properties and pH dependent swelling and dissolving properties [6, 7] and had been previously used for drug delivery like mucoadhesive microsphere [6], mucoadhesive film [7], nanoparticle [14] and prolonged gastric delivery system [15]. But studies about the application of this complex to pharmaceutical excipients were not reported.

The purpose of this study is to prepare chitosan/Carbopol IPC powder as pharmaceutical excipients and make the extended release tablet containing IPC. The release mechanism of drug from the tablet containing IPC was also evaluated. Theophylline was selected as a model drug, because it had been used as a model drug in many other researches to prepare the sustained release tablet [16-18]. The tablet containing IPC which had a swelling property was expected to extend the release of theophylline. And chitosan with different molecular weight (low, medium and high Mw) was used in preparing IPC to

control the release profile of drug.

2. Materials and methods

2.1. Materials

Theophylline anhydrous and Chitosan (low, medium and high Mw) were purchased from Sigma-Aldrich (St. Louis, MO). Carbopol 971 was supplied by BF Goodrich Co. (Cleveland, Ohio, USA). Hydroxymethylcellulose (HPMC) 2910 was obtained from Samsung Fine Chemicals (Seoul, Korea). All other chemicals were of reagent grade or above and were used without further purification.

2.2. Preparation of chitosan/Carbopol IPC

Carbopol 1mg/ml aqueous solution and chitosan 5mg/ml solution in acetic acid were mixed together. The resulting precipitate (Carbopol/chitosan IPC) was obtained, washed with distilled water, and dried under the vacuum for 24 h. The dried complex was ground by the grinder and ball mill. The obtained powder was passed through 200 μm sieve.

2.3. FT-IR spectroscopy study

Infrared absorption spectra of the chitosan, Carbopol and their complex were obtained using a FT-IR spectrophotometer (LX30-7012, Perkin Elmer). The samples were pressed into the potassium bromide pellet prior to obtaining their

IR absorption spectra.

2.4. Differential scanning calorimetry (DSC)

Thermal analysis was carried out using a differential scanning calorimeter (DSC 50, Shimadzu Scientific Instruments, MD). The samples of 5 mg were placed in an aluminium sealed pan, and heated at a scanning rate of 10^{o}C/min from 40 to 450^{o}C. The samples were preheated up to 200^{o}C in order to remove residual water.

2.5. Transmittance measurements

The ratio of chitosan/Carbopol in the complex was investigated by monitoring the transmittance of solution at a wavelength of 600 nm using a spectrophotometer (UV-1601, Shimadzu, Japan). Chitosan acetic acid solutions (0.5, 1 and 2 mM) and Carbopol aqueous solutions (0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4 mM) were used. The concentration was calculated by dividing the weight of chitosan and Carbopol by the molecular weight of each monomer unit. Each of chitosan solution (3ml) was mixed Carbopol solutions (3ml) and shaked vigorously. Then, it left 10min before measuring the transmittance as a function of various mixing ratios (chitosan/Carbopol).

2.6. Preparation of theophylline tablet

Theophylline tablets with the total weight of 250 mg were compressed

from the mixture of theophylline and an excipient at 1:1 mixing ratio by using a hydraulic press with 13-mm diameter. The compression force was fixed at 10 kN/cm^2 with a dwell time of 1 s. Carbopol, chitosan, HPMC 2910 and three kinds of chitosan/Carbopol IPC (three different molecular weight of chitosan) were used as the excipients.

2.7. Dissolution test of theophylline from the tablet

Dissolution test was carried out using a dissolution tester (DST 810, Labfine, Inc., Korea). Theophylline tablets were placed on the mash in 900 ml of the pH 1.2 and pH 6.8 medium at 37^oC using the USP dissolution apparatus II (paddle method) with a paddle rotating at 50 rpm. The samples were withdrawn at predetermined time intervals and then analyzed using HPLC system (Shimadzu Scientific Ins., Japan) at the wavelength of 280nm with the flow rate of 1.2 ml/min (Mobile phase; 100 mM acetate buffer/acetonitrile = 93/7,v/v%).

2.8. Determination of matrix erosion and water uptake

Matrix erosion and water uptake were evaluated 250mg tablet containing high molecular weight chitosan/Carbopol IPC. The tablets were placed in 900 ml of the pH 1.2 and pH 6.8 mediums at 37^oC using the USP dissolution apparatus II (paddle method) with a paddle rotating at 50 rpm. The tablets were withdrawn at predetermined time intervals and weighed after removing the

surface medium with kimwipes®. Weighed tablet dried under the vacuum for 24 h. Next, weight of dried tablet was measured. The water uptake ratio and matrix erosion were calculated using follow equations.

$$\text{Water uptake (\%)} = (W_h - W_d) / W_d * 100 \quad (1)$$

$$\text{Matrix erosion (\%)} = (W_i - W_d) / W_i * 100 \quad (2)$$

Where W_h is weight of hydrated tablet, W_d is weight of dried tablet and W_i is initial weight of tablet. W_d was calculated by subtracting the weight of solute in the absorbed medium from the measured weight right after drying.

3. Results and discussions

3.1. Characterization of chitosan/Carbopol IPC

2-aminoglucose and 2-acetaminoglucose unit were confirmed by the band at 1655 and 1570 cm^{-1} in the IR spectrum of chitosan in Fig. 1 [19], because of the raw chitosan having a degree of deacetylation of 85%. The peak at 1715 cm^{-1}in the IR spectrum of Carbopol was ascribed to C=O stretching of carboxylic group. In comparison with chitosan and Carbopol IPC showed significant change in IR spectrum. After forming complexes, the band corresponding to NH_3^+ group at 1640 cm^{-1} was observed [20] and the bands attributing to the symmetrical and asymmetrical stretching of COO^- group at 1550 and 1408 cm^{-1} were also observed [21]. These results indicated that the chitosan/Carbopol IPC(powder prepared by precipitating in solution) was formed by the electrostatic interaction between COO^- group of Carbopol and NH_3^+

group of chitosan. The peak attributing to C=O stretching of carboxylic group was also observed in the chitosan/Carbopol IPC powder, because the carboxylic acid of Carbopol, which was not dissociated still remained in the complex. When complexes were formed with different Mw of chitosan, no difference of IR spectra was observed indicating that the same mechanism is associated in forming complex. So the complex of high Mw chitosan and Carbopol IPC was used in the further characterization experiments.

Fig. 2 shows the DSC thermograms of the chitosan, Carbopol and their complex. The first scan of all samples showed an endotherm peak between 70 and 110^{o}C corresponding to the evaporation of the moisture content (data not shown). An exothermal peak which is corresponded to the decomposition (thermal and oxidative) of chitosan appeared in around 320^{o}C in the second heating of chitosan [22, 23]. In DSC curve of Carbopol, endothermal peaks which are correlated to the glass transition temperature and decomposition temperature were shown at approximately 135 and 280^{o}C, respectively [24, 25]. While these peaks showed in chitosan or Carbopol disappeared in the DSC curve of chitosan/Carbopol IPC, new broad peak around 385^{o}C was observed. The thermograms indicated that chitosan/Carbopol IPC which had different thermal characteristics compared with raw materials was obtained by precipitation in aqueous solution.

The transmittance change of the solution was measured as a function of mixing ratio of chitosan and Carbopol to determine the composition of IPC

(Fig. 3). Every chitosan acetic acid solution and Carbopol aqueous solution was completely clear. Setting the standard of comparison to mixing ratio of 1/1, when the concentration of chitosan was increased, no change of transmittance was observed. Because of saturation of the reaction site of Carbopol, added chitosan could not react with Carbopol. This result indicated that Carbopol was a rate limiting material in forming an IPC. When the concentration of Carbopol was increased, the transmittance sharply decreased up to mixing ratio of 1/4. For the reason that the amount of formed an IPC increase up to mixing ratio of 1/4 and then the reaction site of chitosan was saturated. After that point, excess amount of Carbopol could not react with chitosan. This clearly indicates that optimal complexation ratio of chitosan/Carbopol was 1/4. The reason of that the complexation ratio was not 1/1 but 1/4 was degree of dissociation. The measured pH of prepared chitosan acetic acid solution and Carbopol aqueous solution were 3.4 and 3.9, respectively. And the pKa value of chitosan and poly(acrylic acid) were 6.5 and 4.7 (Carbopol is a polymer of acrylic acid and slightly crosslinked, so regard pKa of PAA as pKa of Carbopol) [26]. The ratio of ionized Carbopol and chitosan calculated from the Henderson-Hasselbalch equation (3) were 13.7% and about 100%, respectively.

$$pH = pKa + \log[A^-]/[HA] \quad (3)$$

The theoretical ratio of complexation of chitosan and Carbopol was 1/7, but many other factors like, crosslinking agent of Carbopol, degree of deacetylation of chitosan, ionic strength and steric hindrance could affect to form a complex

in real situation. Therefore, the obtained result (1/4) was a little different from theoretical value (1/7).

3.2. In vitro drug release study

The release profiles of theophylline from the directly compressed tablets containing various excipients in pH 6.8 medium were shown in Fig. 4. During the dissolution test, every formulation showed swelling property, except a tablet containing chitosan. The characteristics of chitosan such as flake shape, fast water uptake and capillary action induced quick disintegration of the chitosan tablet within 10 minutes. It caused complete drug release within 30 minutes in pH 6.8 medium. In case of tablet containing HPMC, soluble and non-ionizable excipient, it extended release of theophylline to 12h with significant burst effect. The initial burst effect was observed in the tablet consisting of chitosan or HPMC. In the presence of Carbopol, drug was completely released within 12h. The tablet containing Carbopol showed a zero-order release profile as reported in other literature [11, 12]. The main event of these dissolution tests was an extended release profile of tablet containing chitosan/Carbopol IPC. The drug was diffused out of the IPC matrix tablet slower than tablet consisting of chitosan, Carbopol or HPMC. Since chitosan/Carbopol IPC didn’t dissolve in pH 6.8 medium but had a swelling property, drug was continuously released out of IPC tablet up to 20 h as expected. It might have taken some time for the drug within the matrix to diffuse out through the gap between the swelled

IPC particles.

Fig. 5 showed release profiles conducted in pH 1.2 medium. The tablet with chitosan also showed fast release profile in this medium. But, the drug release from chitosan tablet in pH 1.2 medium was slower than that in pH 6.8 medium, otherwise the drug release from other tablet was faster than that in pH 6.8 medium, because chitosan was dissolved in acidic condition and formed a viscous gel. All tested tablets except chitosan showed similar release profiles, but drug release from IPC tablet was little more sustained compared with Carbopol and HPMC.

The photographs of theophylline tablet consisting of IPC during dissolution test were shown in Fig. 6. From those photographs, it was observed that IPC tablet in the pH 6.8 medium maintained the appropriate strength and contained drug in the core region after 12h. On the other hand, tablet in the pH 1.2 medium converted to transparent tablet and disappeared drug in the core region after 8h. And the swelling was faster in pH 1.2 medium than 6.8.

It was anticipated that drug release was controlled by changing the Mw of chitosan. Nevertheless, when IPC were formed with different Mw of chitosan, little difference was observed in dissolution profiles at pH 1.2 and 6.8 mediums. It was reasoned that, as the content of chitosan in the IPC was small (30~40 w/w%) and Mw of chitosan couldn’t affect on the release profiles, remarkably.

3.3. Evaluation of drug release mechanism

To determine the release kinetics, the experimental data was fitted to the Kosmeyer and Peppas model [27] (Eq. 4) and obtained release parameter were shown in Table 1.

$$M_t/M_\infty = kt^n \quad (4)$$

where, M_t/M_∞ is the fractional solute release, t is the release time, k is a kinetic constant characteristic of the drug/polymer system and n is an exponent which characterizes the mechanism of release of the drug. n=0.5 for Fickian diffusion (molecular diffusion of the drug due to a chemical potential gradient) or Case I, 0.5<n<1.0 for anomalous diffusion or non-Fickian release, n=1.0 for relaxational release (associated with stresses and state transition in hydrophilic glassy polymer) or Case II release. The release parameters were obtained by fitting up to first 60 % of drug release [27, 28]. In all analyses the fitting results were reliable with high correlation coefficients and release profile of chitosan tablet couldn't fit to the equation since the drug release was too fast. The n value of HPMC in pH 6.8 and 1.2 were 0.46and 0.76, respectively. The release mechanism in pH 6.8 medium couldn't explain since n value of below 0.5 wasn't characterized and that in pH 1.2 medium was anomalous diffusion. This indicates that more than one mechanism may be involved. In case of Carbopol, the n value suggested that relaxational release occurred in pH 6.8 medium and anomalous diffusion occurred in pH 1.2 medium. This can be explained by the properties of Carbopol which formed a sticky gel and dissolve

more readily in high pH and formed a watery gel and slightly dissolve in low pH. Contrary to HPMC and Carbopol which had anomalous release mechanism in some medium, tablet consisting of chitosan/Carbopol IPC showed just one release mechanism according to the pH. The n value of chitosan/Carbopol IPC were 0.57 and about 0.89 in pH 6.8 and 1.2 medium, respectively. The IPC tablet showed diffusional release mechanism in pH 6.8, probably due to the poorly water solubility and great swelling property of IPC in high pH. And relaxation release mechanism was shown in pH 1.2 medium, since IPC was dissolved and tremendously swelled in acidic condition.

Although Kosmeyer model had been used to evaluate the release mechanism, to determine the mechanism more precisely Peppas and Sahlin model [29] (Eq. 5) was introduced.

$$M_t/M_\infty = k_1 t^m + k_2 t^{2m} \quad (5)$$

where, M_t/M_∞ is the fractional solute release, t is the release time, k_1 and $k_2$represent kinetic constants related with diffusional and relaxational release, respectively. And m is the purely Fickian diffusion exponent for a device of any geometry shape. The aspect ratio (8.1) was calculated by dividing the diameter of tablet (13mm) by the thickness (1.61mm). From the aspect ratio, the Fickian diffusion exponent (0.465) was obtained [29]. Table 2. showed the release parameters obtained from Eq. 5. This result also had high correlation coefficients. It was more precisely confirmed that diffusional release and relaxational release were predominant in IPC tablet at pH 6.8 and 1.2 medium,

respectively. And other parameters show similar result with Table 1.

To confirm the release mechanism by experiment, water uptake and erosion of chitosan/Carbopol IPC 250 mg tablet were tested and the results were present in Fig. 7. The swelling behavior of IPC tablet was different from the pH of medium. In pH 6.8 medium the degree of swelling was about 1300 % and the hydrated tablet had appropriate hardness after 8 h. However, IPC matrix didn’t erode in pH 6.8 for 8 h. These unique characteristics of chitosan/Carbopol IPC made drug diffuse out through the gap in 6.8 medium. The degree of swelling was over 2000 % in pH 1.2 medium after 8 h and it was changed to transparent and weak tablet. Furthermore, IPC matrix was eroded about 25 % for 8 h. The linear drug release from IPC was attributed to synchronization between swelling and erosion of polymer like as reported by Lee and Peppas [30].

4. Conclusions

Chitosan/Carbopol IPC has a merit for pharmaceutical excipients in extended or sustained release matrix systems, due to the characteristics of Chitosan/Carbopol IPC such as swelling with no erosion in pH 6.8 medium. The main release mechanisms of complex tablet were diffusional release in pH 6.8 medium and relaxation of polymer in pH 1.2. So, when IPC matrix was used in controlled drug delivery in specific organ such as gastric delivery or intestinal delivery, our system was convenient to control the drug release,

because just one mechanism was involved.

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Table 1. Parameter estimates derived from the fitting Eq. (1) to experimental data reported by Korsmeyer et al. (1983).

pH 6.8 medium	k	n	b	R^2	Release amount (%) of last time
HPMC	0.3505	0.4589	-0.0027	0.9997	67
Carbopol	0.1271	0.9146	0.0047	0.9992	46
L. IPC	0.1708	0.5704	-0.0039	0.9999	55
M. IPC	0.1949	0.5671	-0.0026	0.9999	62
H. IPC	0.1889	0.5730	-0.0023	0.9999	62
pH 1.2 medium	k	n	b	R^2	Release amount (%) of last time
HPMC	0.2222	0.7603	0.0033	0.9997	64
Carbopol	0.2470	0.6767	-0.0005	1.0000	63
L. IPC	0.1563	0.8908	0.0042	0.9995	54
M. IPC	0.1539	0.8698	0.0033	0.9997	52
H. IPC	0.1481	0.9269	0.0037	0.9997	54

Table 2. Parameter estimates derived from the fitting Eq. (2) to experimental data reported by Peppas and Sahlin. (1989).

pH 6.8 medium	k_1	k_2	R^2	Release amount (%) of last time
HPMC	0.3273	0.0.49	1.0000	67
Carbopol	0.0161	0.1170	0.9993	46
L. IPC	0.1397	0.0281	0.9993	55
M. IPC	0.1667	0.0282	0.9995	62
H. IPC	0.1601	0.0291	0.9995	62
pH 1.2 medium	k_1	k_2	R^2	Release amount (%) of last time
HPMC	0.1021	0.1233	0.9999	64
Carbopol	0.1505	0.0953	0.9998	63
L. IPC	0.0262	0.1353	0.9996	54
M. IPC	0.0323	0.1256	0.9998	52
H. IPC	0.0096	0.1432	0.9997	54

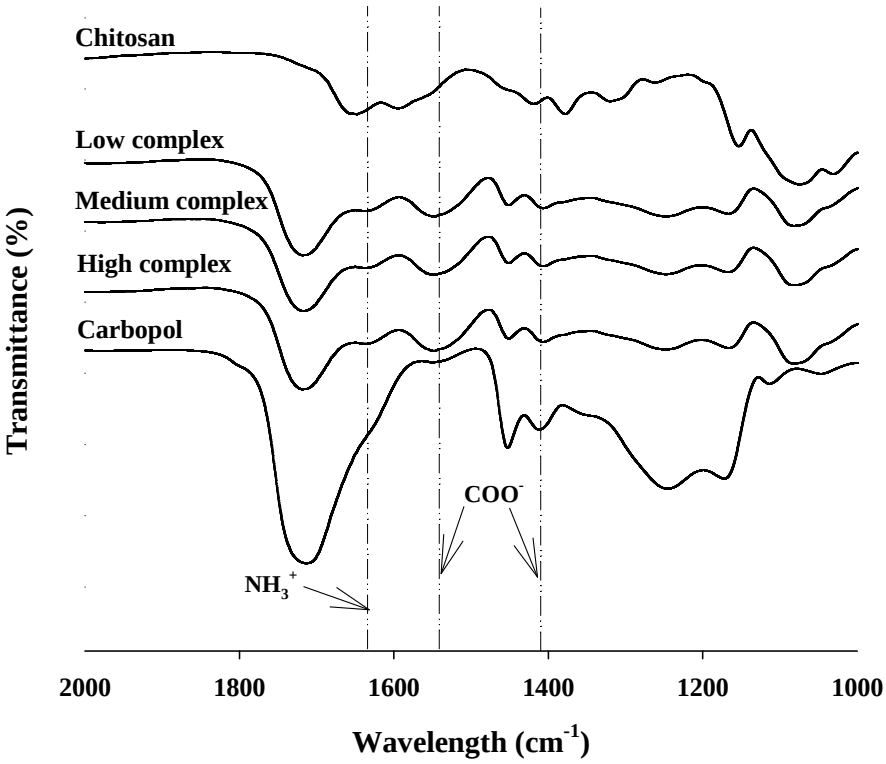


Fig. 1. FT-IR spectra of chitosan, Carbopol and chitosan/Carbopol interpolymer complexes (IPC) with various molecular weight of chitosan

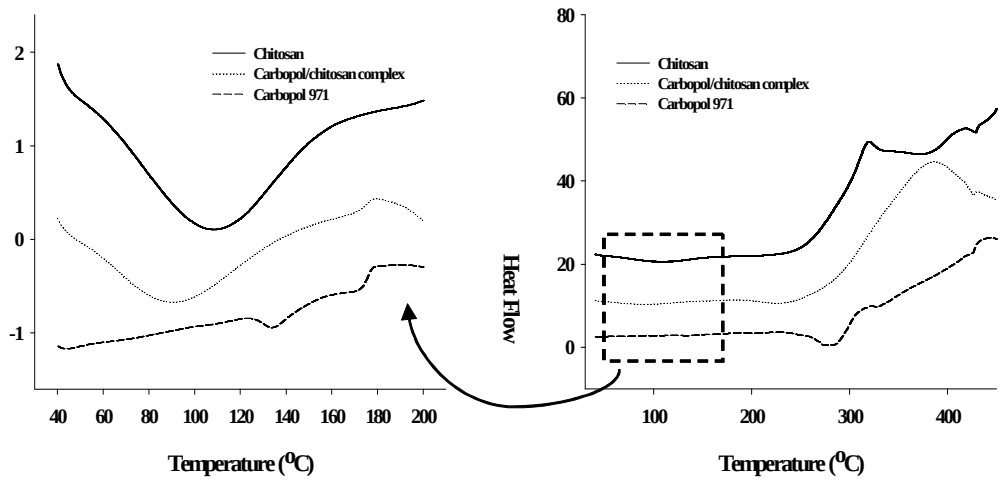


Fig. 2. Comparison of the DSC thermogram of the chitosan/Carbopol interpolymer complex (IPC) with those of chitosan and Carbopol.

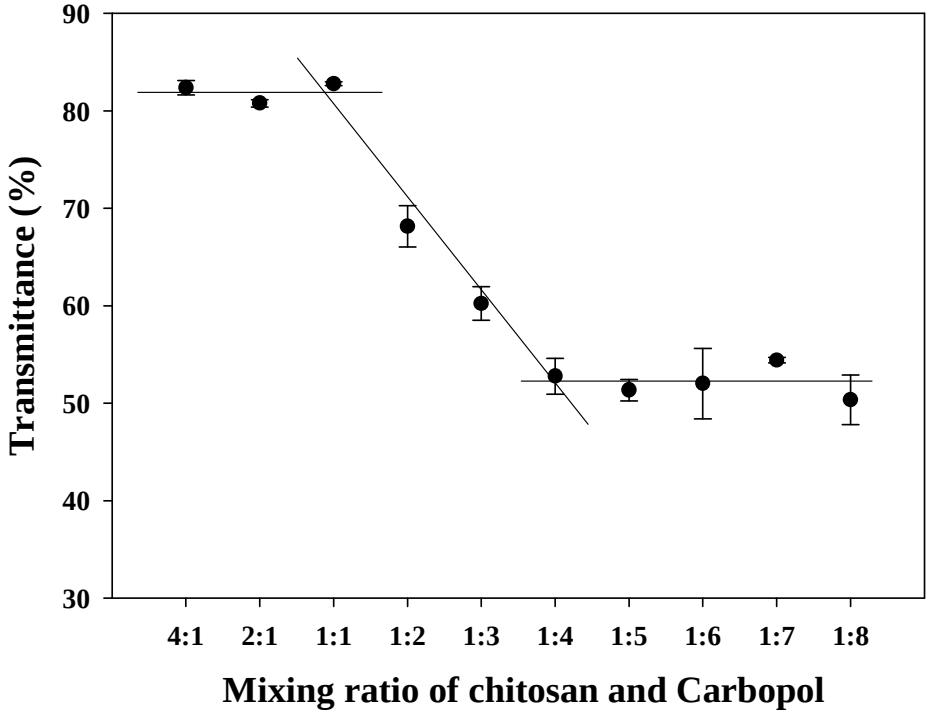


Fig. 3. Effect of the ratio of Carbopol 971 and chitosan on the transmittance of the solution

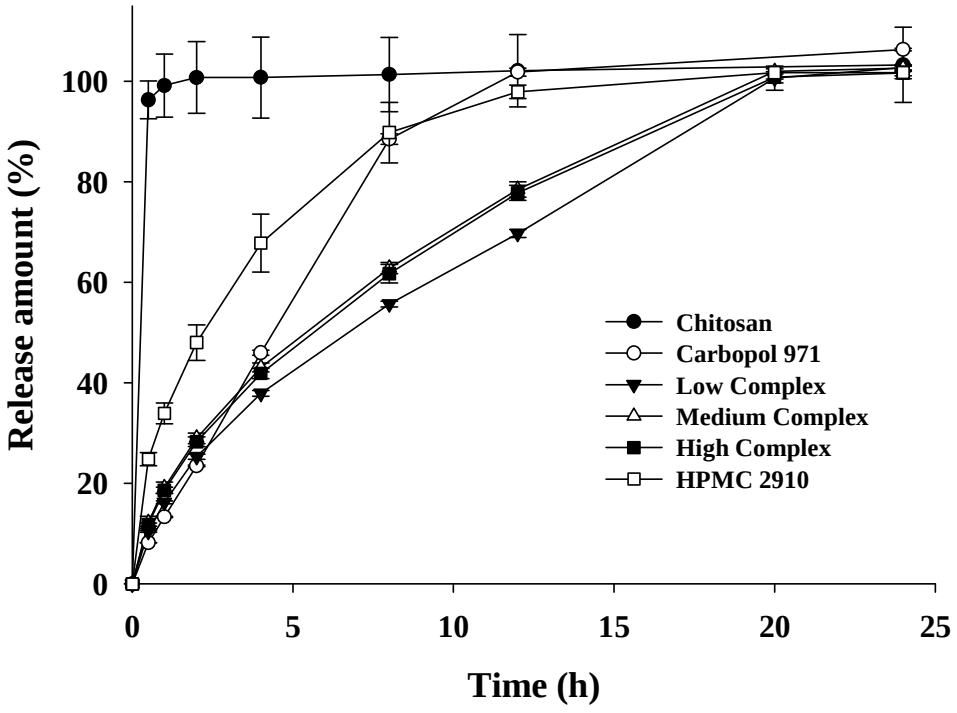


Fig. 4. Release profiles of theophylline from the tablets consisting of various excipients in pH 6.8.

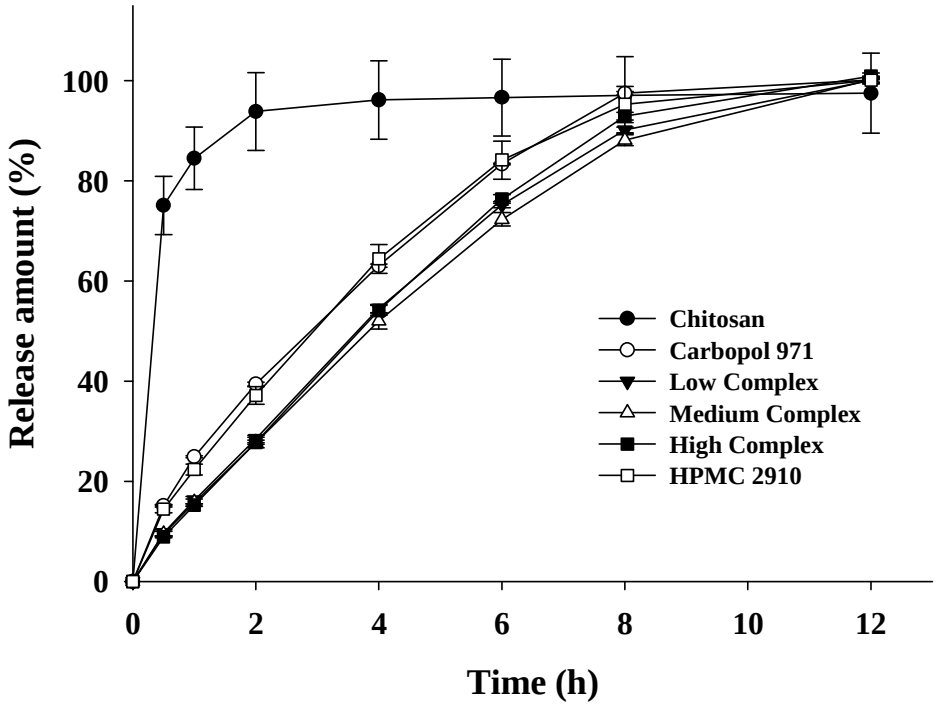


Fig. 5. Release profiles of theophylline from the tablets consisting of various excipients in pH 1.2.

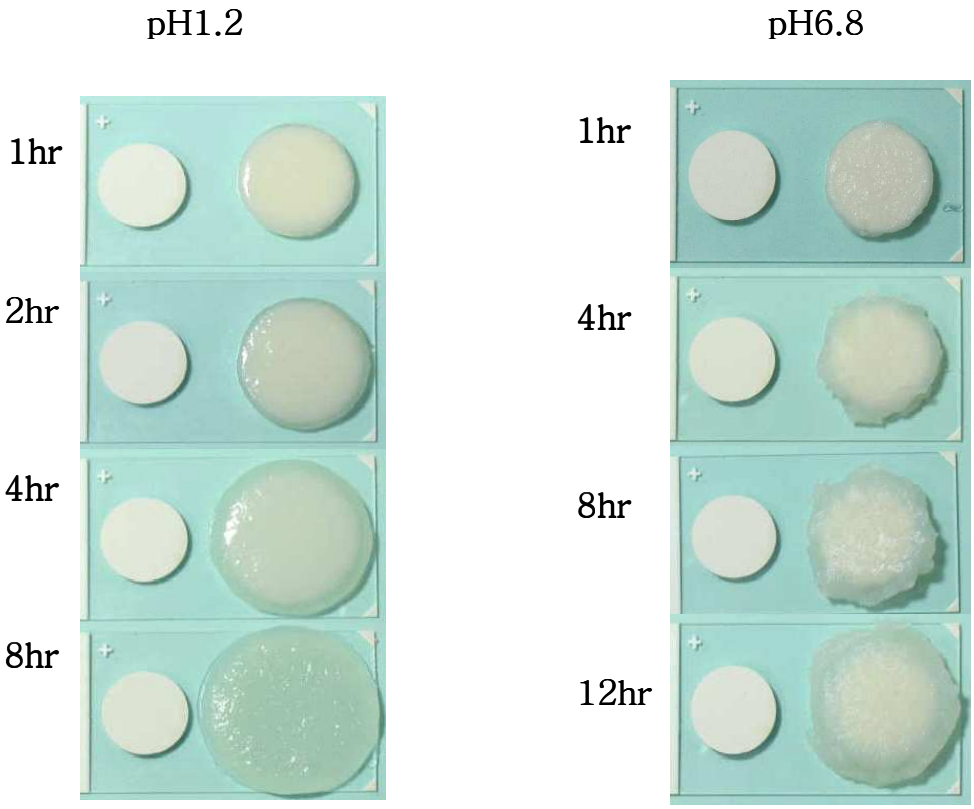
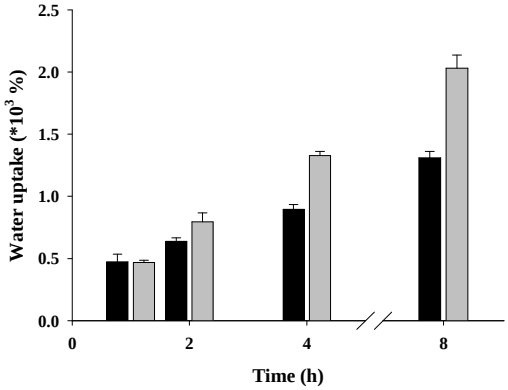


Fig. 6. Effect of the pH of the medium on the swelling and dissolution of the theophylline tablet containing chitosan/Carbopol interpolymer complex

(A)



(B)

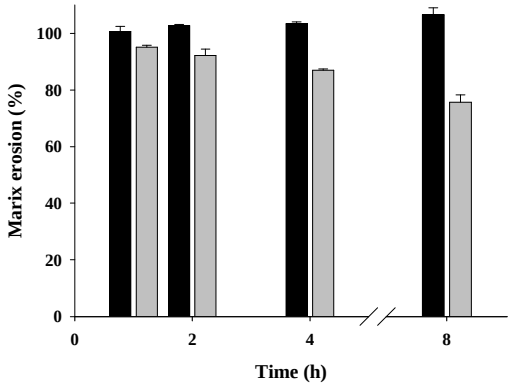


Fig. 7. Water uptake (A) and matrix erosion (B) of tablet containing 250mg chitosan/Carbopol interpolymer complex (IPC) in pH 1.2 (gray column) and 6.8 buffer (black column).